OL Organic Letters
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

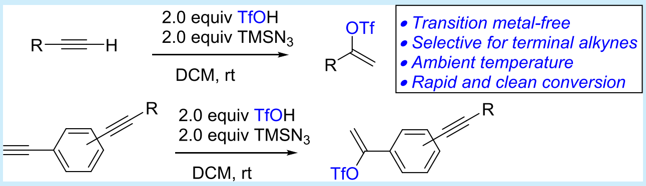
Chemoselective Synthesis of 1,1-Disubstituted Vinyl Triflates from Terminal Alkynes Using TfOH in the Presence of $TMSN_3$

Jumreang Tummatorn,*[,‡,§] Kunlayanee Punjajom,[§] Warabhorn Rodphon,[§]
Sureeporn Ruengsangtongkul,[‡] Nattawadee Chaisan,[§] Kanyapat Lumyong,[‡]
Charnsak Thongsornkleeb,[†,§] Phongprapan Nimnual,[§] and Somsak Ruchirawat[‡,§]

[†]Laboratory of Organic Synthesis, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand
[‡]Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand
[§]Program on Chemical Biology, Chulabhorn Graduate Institute, Center of Excellence on Environmental Health and Toxicology (EHT), Ministry of Education, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand

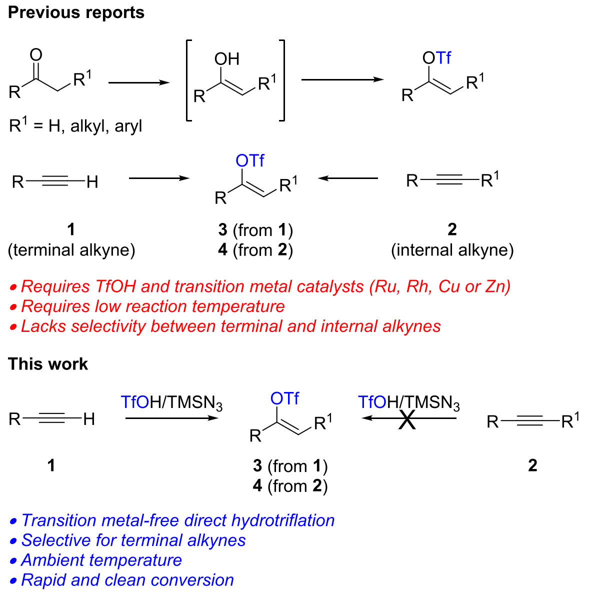
Supporting Information

ABSTRACT: 1,1-Disubstituted vinyl triflates are synthesized by direct hydrotriflation of terminal alkynes employing a combination of TfOH and $TMSN_3$ in DCM at room temperature. Interestingly, under these conditions, only terminal alkynes were selectively converted to the corresponding vinyl triflates, while internal alkynes were not reacted. A broad range of substrates were successfully converted to the corresponding 1,1-disubstituted vinyl triflates in good to excellent yields even those with internal alkyne moieties present in the molecules.



Vinyl triflate is an important functional group used in many synthetic transformations, especially for cross-coupling reactions including C−C,[1] C−O,[2] C−N,[3] and C−halogen[4] bond formations. The most general method for preparing vinyl triflate derivatives is the trifluoromethanesulfonylation or triflation of enolates using various triflating agents.[5] However, only a few reported methods employed alkynes as starting materials in spite of their ease of access (Scheme 1). In fact, the conditions using trifluoromethanesulfonic or triflic acid (TfOH) as the hydrotriflating agent has been reported.[6,7,4b] However, most reactions needed to be carried out under low temperatures[8] to avoid solvolysis of the vinyl triflate product.[9] In addition, this method has no particular chemoselectivity toward the alkyne substrates; both internal and terminal alkynes could be converted to vinyl triflates nonselectively. A similar lack of selectivity was also observed when using rhodium,[10] ruthenium,[11] copper,[12] and zinc[13] complexes as the catalysts. Therefore, development of a new method for controlling chemoselectivity of hydrotriflation of alkynes is a challenging task. In this work, we discovered that combination of $TMSN_3$ and TfOH reagents could chemoselectively convert only the terminal alkynes to 1,1-disubstituted vinyl triflates at room temperature. This combination essentially lowered the reactivity of TfOH in hydrotriflation on internal alkynes, resulting in only trace amount of trisubstituted vinyl triflates while terminal alkynes readily reacted to give 1,1-disubstituted vinyl triflates in good conversion with no formation of the corresponding vinyl azides. This novel mode of reactivity observed in combination of TfOH and $TMSN_3$ was envisioned to be a potentially useful tool for chemical synthesis, especially when the reaction is performed on compounds containing both internal and terminal alkynes.

Scheme 1. Methods for the Synthesis of Vinyl Triflates

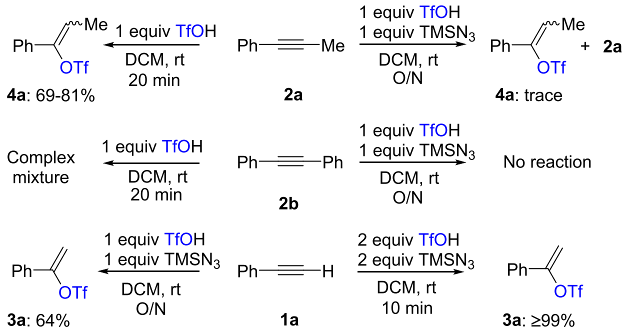


To elaborate on these findings, reactions were performed with various internal alkynes as shown in Scheme 2. The

Received: May 5, 2019

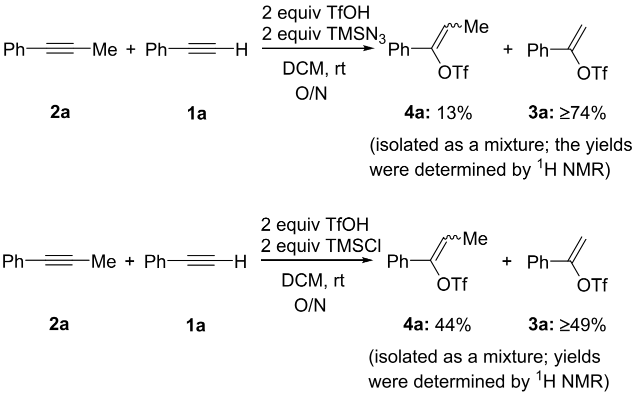
DOI: 10.1021/acs.orglett.9b01576
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Initial Reaction Evaluations



reaction of methylphenylacetylene (**2a**) with 1.0 equiv each of TMSN$_3$ and TfOH offered vinyl triflate in only trace amount whereas using TfOH alone could provide the corresponding products (**4a**) as an isomeric mixture in good combined yields (69−81%).[7] When using diphenylacetylene (**2b**) as the starting material, no reaction was observed with 1.0 equiv each of TfOH and TMSN$_3$ even after stirring overnight, whereas the reaction between **2b** with 1.0 equiv of TfOH alone resulted in the decomposition within 20 min. These results highlighted the essential role of TMSN$_3$ in lowering the reactivity of TfOH in the current protocol. To optimize the conditions, phenylacetylene (**1a**) was used as the screening substrate.[14] Using 1.0 equiv each of TMSN$_3$ and TfOH, the reaction provided the desired product (**3a**) in 64% yield. After further optimization, product **3a** could be obtained in quantitative yield when 2.0 equiv each of TMSN$_3$ and TfOH were employed in DCM at room temperature for 10 min. To probe the chemoselectivity of this protocol, a 1:1 mixture of compounds **1a** and **2a** was subjected to the optimal conditions employing TMSN$_3$ (2.0 equiv) and TfOH (2.0 equiv) in DCM at room temperature for overnight. This reaction provided vinyl triflate **3a** as the major product in 74% yield, while product **4a** (from **2a**) was obtained in only 13% yield even after an overnight stirring. In addition, several additives were also screened for this transformation. Apparently, the combination of TfOH and TMSCl could smoothly provide the desired product at room temperature. However, no chemoselectivity was observed when using this combination. The results showed that the selectivity of hydrotriflation dropped to almost 1:1 ratio of **3a** and **4a** as shown in Scheme 3. Therefore, a combination of 2.0 equiv each of TMSN$_3$ and TfOH in DCM at room temperature was the optimal conditions for the chemoselective hydrotriflation of terminal alkynes to give 1,1-disubstituted vinyl triflates.

Scheme 3. Crossover Experiments of Internal and External Alkynes

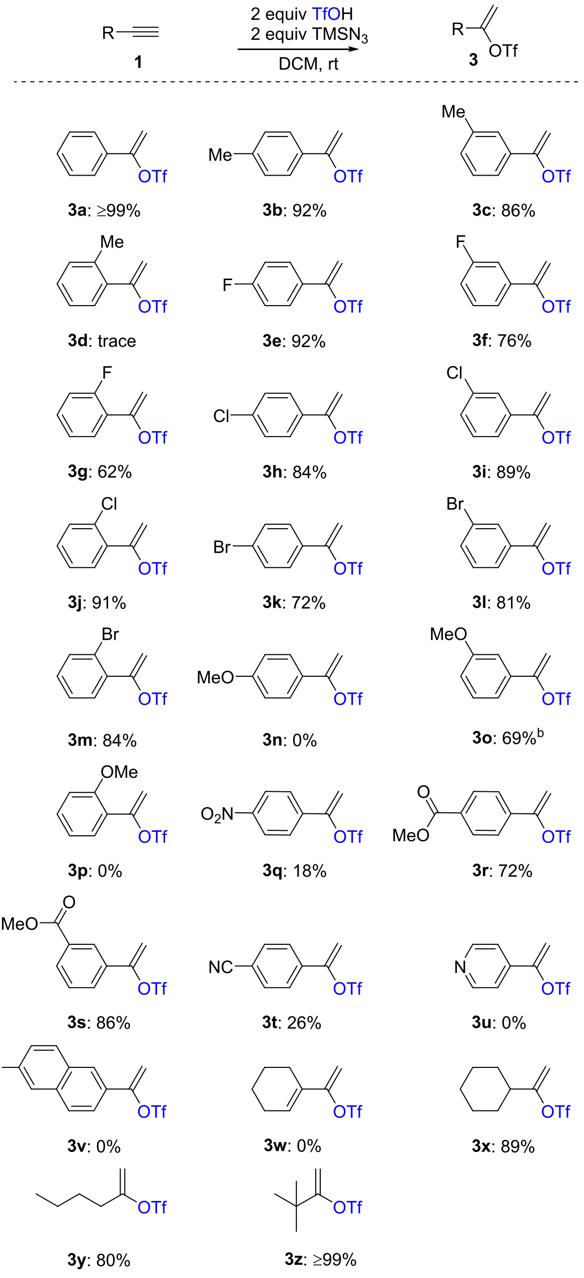


(isolated as a mixture; the yields were determined by ^{1}H NMR)

(isolated as a mixture; yields were determined by ^{1}H NMR)

Having the optimal conditions for the synthesis of vinyl triflates in hands, our attention was turned to study the scope of the reaction (Scheme 4). The utility of this method was probed with substrates containing terminal alkynes. The reaction of phenylacetylene (**1a**) produced product **3a** in quantitative yield. With electronically neutral substrates as in *p*- and *m*-tolylacetylene (**1b** and **1c**), the reactions furnished the corresponding vinyl triflates **3b** and **3c** in excellent yields. However, *o*-tolylacetylene (**1d**) proved incompatible under

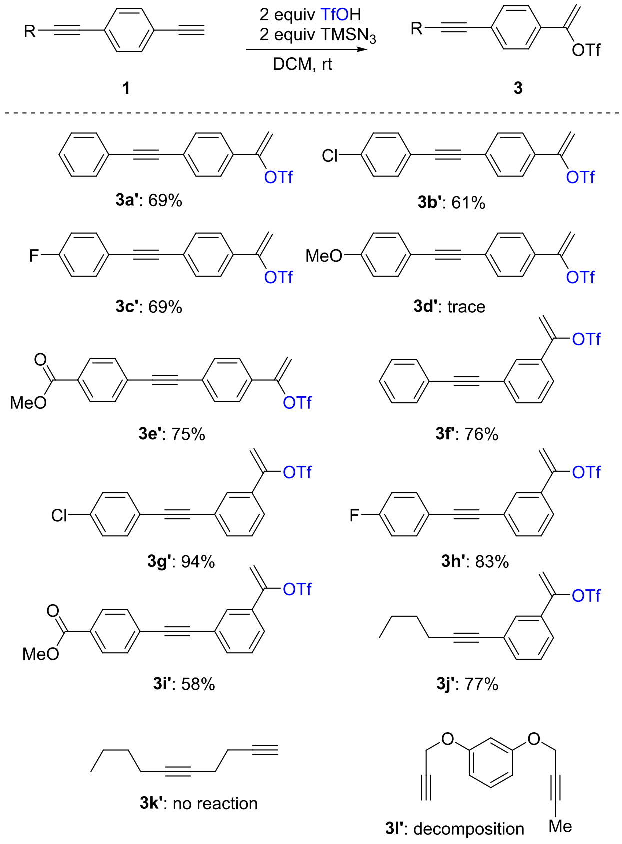
Scheme 4. Substrate Scope for the Synthesis of Vinyl Triflates from Terminal Alkynes[a]



[a]Isolated yields. [b]Yield was determined by ^{1}H NMR of an inseparable mixture of product and starting material.

these conditions; the reaction resulted in decomposition of **1d** and only trace amount of product **3d** was observed. Then, halogen substituted phenylacetylene derivatives, including fluorine, chlorine, and bromine substituents, were examined. The reactions of *p*-, *m*-, and *o*-fluorophenylacetylenes provided the desired products (**3e**−**g**) in moderate to excellent yields (62−92%). The reactions also proceeded excellently for *p*-, *m*- and *o*-chlorophenylacetylenes (**1h**−**j**), furnishing the desired products all in excellent yields (**3h**−**j**). Similar results were also observed in the bromine analogues; substrates **1k**−**m** were transformed to the corresponding vinyl triflates **3k**−**m** in excellent efficiencies. Unfortunately, *p*- and *o*-methoxy-substituted substrates (**3n** and **3p**) decomposed under the reaction conditions. However, the reaction of *m*-methoxy substrate (**1o**) was uneventful; the substrate was transformed to the corresponding vinyl triflate (**3o**) in 69% yield. For this substrate, we also employed conditions previously reported by others using only TfOH in DCM for comparison to observe only decomposition of the substrate.[7] This result clearly showed the superiority of our method over the previously reported procedure. It also further highlighted the essential role of TMSN$_3$ for the success of the reaction. The methoxy group located at the *meta*-position in **1o** could not delocalize electrons to the vinyl carbocation; therefore, the reactive quinone methide-type species could not be generated, hence the successful reaction. Next, substrates with electron-withdrawing substituents were evaluated. The reaction of *p*-nitro-substituted substrate (**1q**) was incomplete and gave the desired vinyl triflate (**3q**) in low yield, probably due to the generation of the unstable vinyl cation intermediate. With methyl ester substituents, both at the *p*- and *m*-positions (**1r** and **1s**), the reactions provided the vinyl triflate products in 86% and 72% yields, respectively. For *p*-nitrile-substituted substrate (**1t**), the reaction could not go to completion, probably due to the nitrile functional group became protonated by TfOH resulting in only 26% yield of the desired product (**3t**). The latter effect was also observed in pyridine-containing substrate (**1u**), the reaction of which only led to decomposition. Furthermore, we found that alkynylnaphthalene **1v** and alkynylcyclohexene **1w** were incompatible in this reaction and could not be converted to the corresponding vinyl triflates; only decomposition was observed for these compounds. The reaction was next attempted with alkylalkynes. Gratifyingly, the reactions proceeded efficiently to afford the corresponding products (**3x**−**z**) in good to excellent yields (80 to ≥99%).

Scheme 5. Scope of Substrates for the Reaction of Compounds Containing Both Internal and Terminal Alkynes[a,b]

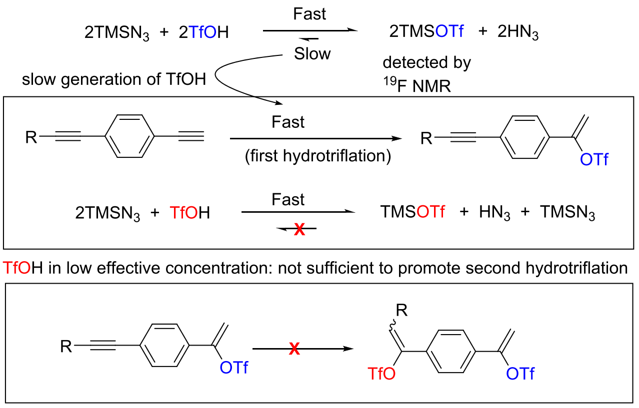


[a]Isolated yields. [b]Reaction time is in parentheses.

Furthermore, a range of substrates containing both internal and terminal alkynes within the same molecules (**1**) was examined as shown in Scheme 5. For compound **1a′** containing only the parent phenyl ring, the reaction proceeded smoothly to give the corresponding product **3a′** in 69% yield. For substrates containing *p*-haloarylalkyne substituents (**1b′** and **1c′**), the reactions also proceeded successfully to give the desired products in 61% and 69% yields, respectively. The reaction of *p*-methoxy-substituted substrate **1d′** was more problematic as it provided the corresponding product (**3d′**) in trace amount. Under strong acidic conditions, the *p*-methoxy substituent could delocalize electrons into the *para*-cationic species, resulting in the formation of quinone methide-type intermediates that could undergo other side reactions; this thus contributed to the lower yield. The decomposition observed in these substrates was similar to that observed for compound **1n** and **1p** in Scheme 4. However, in substrates containing an electron-withdrawing *p*-methyl ester group (**1e′**), the reaction occurred smoothly to produce the corresponding vinyl triflate **3e′** in 75% yield. We next turned our attention to study aryl 1,3-diyne substrates. With *m*-phenylalkynyl phenylacetylene (**1f′**), the reaction underwent a smooth conversion at the terminal alkyne to afford the desired product (**3f′**) in 76% yield. Other substituents on the *m*-arylalkynyl group were next examined. As shown with the chlorine and fluorine substituents in substrates **1g′**−**h′**, the reactions proceeded excellently to furnish vinyl triflates **3g′** and **3h′** in 94% and 83% yields, respectively. As a representative of electron-withdrawing group, compound **1i′** with methyl ester group was next employed as the substrate. Under the optimal conditions, the desired product **3i′** was afforded in 58% yield. Besides the arylalkynyl substituents, the reaction was also tested with the substrate containing alkylalkynyl substituent (**1j′**). This compound could be converted successfully to the desired vinyl triflate **3j′** in 77% yield. Surprisingly, the reaction of dialkynyl substrate **1k′** did not proceed under the optimal conditions, resulting in no reaction, while the reaction of compound **3l′** underwent decomposition.

The mechanism of the reaction is proposed as a working mechanism in Scheme 6. We hypothesized that the reaction of 2.0 equiv each of TMSN$_3$ and TfOH quickly set up an equilibrium with the predominant direction to the right to form TMSOTf and HN$_3$. An experimental study was performed using ^{19}F NMR for monitoring the reaction between TMSN$_3$ and TfOH. The result showed that TMSOTf was rapidly generated in situ corroborating well with the

Scheme 6. Proposed Working Reaction Mechanism



hypothesis.[15] In this equilibrium TfOH was generated slowly in the reverse direction. TfOH present in the reaction then readily added to the terminal alkyne moiety in the starting material to give the desired product. At this point, the remaining ratio of $TMSN_3$ and TfOH was 2:1 which forced the equilibrium to lie even further to the right, effectively reducing the concentration of TfOH in the reaction mixture, resulting in low effective concentration of TfOH and became insufficient to promote the second hydrotriflation. As a result, only terminal alkyne reacted under these conditions.

In conclusion, a chemoselective hydrotriflation protocol of terminal alkynes has been developed. Conversion of only terminal alkynes, in the presence of internal counterparts, to give 1,1-disubstituted vinyl triflates can be achieved with this protocol based on the slow generation of TfOH. The current protocol allowed access to 1,1-disubstituted vinyl triflates from terminal alkynes even in the presence of internal alkynes. The protocol is simple and convenient to conduct and allows access to 1,1-disubstituted vinyl triflates selectively in excellent efficiencies. This method complements well with other existing strategies and methods for the generation of vinyl triflates, especially for generation of the 1,1-disubstituted vinyl triflates.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01576.

Optimization, experimental procedures, spectroscopic data, and NMR spectra of compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jumreang@cri.or.th.

ORCID

Jumreang Tummatorn: 0000-0002-1662-151X
Charnsak Thongsornkleeb: 0000-0003-2653-5137

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research work was supported by Chulabhorn Research Institute, Mahidol University, and the Center of Excellence on Environmental Health and Toxicology, Science & Technology Postgraduate Education and Research Development Office (PERDO), Ministry of Education, and Thailand Research Fund through the Royal Golden Jubilee (RGJ) Ph.D. Program (Grant No. PHD/0217/2558) and Thailand Research Fund (RSA6080085).

■ REFERENCES

(1) (a) Vila, C.; Hornillos, V.; Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Eur. J.* **2014**, *20*, 13078−13083. (b) Scott, W. J.; Pena, M. R.; Sward, K.; Stoessel, S. J.; Stille, J. *J. Org. Chem.* **1985**, *50*, 2302−2308. (c) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459−2465. (d) Ackerman, L. K.; Lovell, M. M.; Weix, D. J. *Nature* **2015**, *524*, 454. (e) Garcia Martinez, A.; Osío Barcina, J.; Colorado Heras, M. d. R.; de Fresno Cerezo, Á. *Organometallics* **2001**, *20*, 1020−1023. (f) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 4815−4818.

(2) (a) Andersson, C. M.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1502−1505. (b) Kwon, H. B.; McKee, B. H.; Stille, J. *J. Org. Chem.* **1990**, *55*, 3114−3118. (c) Vallin, K. S.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537−4542. (d) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Chem. Commun.* **2003**, 2222−2223.

(3) (a) Vallin, K. S.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639−6645. (b) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S. I.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y. *Angew. Chem.* **2011**, *123*, 5792−5795. (c) Stolley, R. M.; Guo, W.; Louie, J. *Org. Lett.* **2012**, *14*, 322−325.

(4) (a) Shen, X.; Hyde, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14076−14078. (b) Shirakawa, E.; Imazaki, Y.; Hayashi, T. *Chem. Commun.* **2009**, 5088−5090.

(5) (a) Maity, P.; Lepore, S. D. *J. Org. Chem.* **2009**, *74*, 158−162. (b) Ritter, K. *Synthesis* **1993**, *1993*, 735−762. (c) Specklin, S.; Bertus, P.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 7845−7848. (d) Hargrove, R. J.; Stang, P. J. *J. Org. Chem.* **1974**, *39*, 581−582. (e) Stang, P. J.; Anderson, A. G. *J. Am. Chem. Soc.* **1978**, *100*, 1520−1525. (f) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107−114.

(6) (a) Dhakal, B.; Bohé, L.; Crich, D. *J. Org. Chem.* **2017**, *82*, 9263−9269. (b) Howells, R.; Mc Cown, J. *Chem. Rev.* **1977**, *77*, 69−92.

(7) Lee, P. H.; Park, S. J.; Kim, J. S.; Lee, G. Y. Method for preparation of alkenyl triflates. Repub. Korean Kongkae Taeho Kongbo, KR 2014098468, Aug 8, 2014.

(8) Wu, J.-J.; Xu, J.; Zhao, X. *Chem. Eur. J.* **2016**, *22*, 15265−15269.

(9) (a) Summerville, R. H.; Senkler, C. A.; Schleyer, P. V. R. *J. Am. Chem. Soc.* **1974**, *96*, 1100−1110. (b) Stang, P. J.; Summerville, R. *J. Am. Chem. Soc.* **1969**, *91*, 4600−4601.

(10) (a) Yang, Y.; Moschetta, E. G.; Rioux, R. M. *ChemCatChem* **2013**, *5*, 3005−3013. (b) Yang, Y.; Chang, J.-W.; Rioux, R. M. *J. Catal.* **2018**, *365*, 43−54.

(11) Ouyang, Y.; Xu, X.-H.; Qing, F.-L. *Angew. Chem.* **2018**, *130*, 7042−7045.

(12) (a) Wang, X.; Studer, A. *Org. Lett.* **2017**, *19*, 2977−2980. (b) Suero, M. G.; Bayle, E. D.; Collins, B. S.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332−5335.

(13) Al-huniti, M. H.; Lepore, S. D. *Org. Lett.* **2014**, *16*, 4154−4157.

(14) See the Supporting Information for additional optimization studies.

(15) Nimnual, P.; Tummatorn, J.; Boekfa, B.; Thongsornkleeb, C.; Ruchirawat, S.; Piyachat, P.; Punjajom, K. *J. Org. Chem.* **2019**, *84*, 5603−5613. Also see the Supporting Information for ^{19}F NMR experimental study in the formation of TMSOTf in situ.